

Pharmacologically acceptable salts of Clopidogrel

The present invention refers to salts of Clopidogrel, especially new polymorphic forms of Clopidogrel-hydrobromide, as well as salts of Clopidogrel with benzene sulfonic acid (besylate), with para-toluene sulfonic acid (tosylate), with Naphthalene-2-sulfonic acid (napsylate) and with oxalic acid (oxalate).

10 Clopidogrel is a known pharmaceutically active compound. Clopidogrel is the dextrorotary S-enantiomer of alfa-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)acetic acid-methyl ester.

15 The present invention also refers to a method of making these compounds and to pharmaceutically active compositions, which contain at least one compound of the present invention in a concentration known per se. The present invention further refers to the use of the new compounds and forms for
20 the preparation of pharmaceutically active compositions, which contain at least one compound of the present invention in a pharmaceutically effective concentration.

EP 0 099 802 discloses the racemic mixture as well as both
25 enantiomeric forms of Clopidogrel. EP 1 087 976 discloses further salts of Clopidogrel.

The present invention refers to six new polymorphic forms of (+)-(S)-Clopidogrel-hydrogenbromide, which are named herein
30 as polymorphic "Form A", polymorphic "Form B", polymorphic "Form C", polymorphic "Form D", polymorphic "Form E", and as polymorphic "Form F", as well as two new polymorphic forms of (+)-(S)-Clopidogrel-napsylate, which are named herein as polymorphic "Form A" and polymorphic "Form B". These
35 polymorphic forms differ from each other in their powder-

roentgen-diagrams (XRPD). The polymorphic forms of Clopidogrel hydrobromide in addition differ from each other by their infrared spectra. In the present description the XRPD-peaks are used for the characterization of the compounds.

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The characteristic XRPD-peaks of Clopidogrel-hydrobromide of the polymorphic forms A, B, C, D, E and F and Clopidogrel napsylate of the polymorphic forms A and B are given in degree 2θ with an exactness of ± 0.2 degree 2θ , and are, as
10 listed in the following Table 1 und Table 2, at the following divergence angles.

Table 1

Clopidogrel hydrobromide Form	Angle [$2\theta^\circ$]:	Relative intensity
A	9.83	medium
	10.35	medium
	19.98	strong
	23.03	strong
B	9.49	medium
	10.39	medium
	12.87	medium
	19.53	strong
C	8.20	strong
	8.92	strong
D	9.76	medium
	10.40	weak-medium
	19.50	strong
	23.01	strong
E	7.72	medium
	9.27	medium
	9.88	medium
	11.91	medium
F	12.48	strong
	15.89	medium
	20.16	strong
	21.97	strong

Table 2

Clopidogrel napsylate Form	Angle [2 θ]:	Relative intensity
A	8.59	medium-strong
	13.55	medium-strong
	19.00	medium-strong
	21.34	strong
B	7.67	medium
	8.41	strong
	9.05	medium
	10.00	medium

Clopidogrel hydrobromide of Form A is obtained either by
5 combining hydrogen bromide (HBr) and Clopidogrel base in a
suitable solvent and subsequent crystallization, or by
recrystallization or crystal transformation from the
suspension of any form of Clopidogrel hydrobromide from a
suitable solvent or mixture of solvents. Suitable solvents
10 are acetone, acetic acid ethyl ester, diisopropylether,
tert.-butyl-methylether, methyl-isobutylketone, dichloro-
methane, toluene, isobutyronitrile, isopropanol, preferably
at temperatures between 18°C and 22°C, using a mixture of
solvents containing methyl-isobutylketone und isopropanol,
15 preferably in a weight-ratio of 4:1.

In this sense the invention refers to a method of making
Clopidogrel hydrobromide of Form A, which is characterized
in that Clopidogrel hydrobromide of any crystalline form is
20 crystallized from a solvent or a mixture of solvents, com-
prising acetone, acetic acid ethyl ester, diisopropylether,
tert.-butyl-methylether, methyl-isobutylketone, dichloro-
methane, toluene, isobutyronitrile, and/or isopropanol, pre-
ferably methyl-isobutylketone and/or isopropanol, preferably
25 in a weight ratio of 4:1, within a temperature range of 18°C
to 22°C.

Clopidogrel hydrobromide of Form B is obtained by combining hydrogenbromide (HBr) and Clopidogrel base in a suitable solvent and subsequent crystallization, preferably by crystallizing from this solution by quickly crossing the
5 saturation curves using techniques such as quick addition of an antisolvents or by evaporation crystallization, or by very quick cooling of the crystallization solution (shock cooling). Suitable solvents are acetone and dichloromethane. Suitable antisolvents are aliphatic hydrocarbons such as
10 heptane or hexane.

The invention refers to a method of making Clopidogrel hydrobromide of Form B, which is characterized in that Clopidogrel hydrobromide of any crystalline form is crystal-
15 lized from a suitable solvent, preferably acetone and/or dichloromethane, by quickly crossing the saturation curve, preferably by quick addition of an antisolvents, preferably of an aliphatic hydrocarbon, preferably heptane and/or hexane, or by evaporation crystallization, or by very quick
20 cooling of the crystallization solution (shock cooling).

Clopidogrel hydrobromide of Form C is obtained either by combining HBr and Clopidogrel base in a suitable solvent and subsequent crystallization or by recrystallization or by
25 crystal transformation from a suspension of any Form of Clopidogrel hydrobromide from a suitable solvent or mixture of solvents. A suitable solvent is acetonitrile.

The invention refers to a method of making Clopidogrel
30 hydrobromide of Form C, which is characterized in that Clopidogrel hydrobromide of any crystalline Form is crystallized from acetonitrile.

Clopidogrel hydrobromide of Form D is obtained by either
35 combining HBr and Clopidogrel base in a suitable solvent and

subsequent crystallization or by recrystallization or by crystal transformation from a suspension of any Form of Clopidogrel hydrobromide from a suitable solvent or mixture of solvents, comprising acetone, acetic acid ethyl ester, diisopropylether, tert.-butyl-methylether, methyl-isobutylketone, - dichloromethane, Toluene, isobutyronitrile and/or isopropanol, preferably methyl-isobutylketone and/or isopropanol, preferably in a weight ratio of 4:1, within a temperature range from 30°C to 60°C.

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The invention refers to a method of making Clopidogrel hydrobromide of Form D, which is characterized in that Clopidogrel hydrobromide of any crystalline Form is crystallized from a solvent or a mixture of solvents, comprising acetone, acetic acid ethyl ester, diisopropylether, tert.-butyl-methylether, methyl-isobutylketone, dichloromethane, toluene, isobutyronitrile and/or isopropanol, preferably methyl-isobutylketone and/or isopropanol, preferably in a weight ratio of 4:1, within a temperature range from 30°C to 60°C.

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Clopidogrel hydrobromide of Form E is obtained either by combining of HBr and Clopidogrel base in a suitable solvent and subsequent crystallization or by crystallization of any Form of Clopidogrel hydrobromide from a suitable solvent or a mixture of solvents. Suitable solvents are mixtures of dichloromethane and aliphatic hydrocarbons. Especially preferred are long crystallization times of up to 24 hours, a working temperature range of 0°C to 25°C and crystallization of Form E by slow evaporation of the lower boiling solvent from the solvent mixture.

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The invention refers to a method of making Clopidogrel hydrobromide of Form E, which is characterized in that Clopidogrel hydrobromide of any crystalline Form is

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crystallized from dichloromethane and/or an aliphatic hydrocarbon with a boiling point of preferably 60°C to 125°C, preferably hexane, heptane or octane, preferably within a temperature range from 0°C to 25°C, or by
5 crystallization by slow evaporation of the lower boiling solvent from the solvent mixture at temperatures within the temperature range of 0°C to 25°C. Preferred are long crystallization times of up to 24 hours.

10 Clopidogrel hydrobromide of Form F is obtained by combining HBr und Clopidogrel base in a suitable solvent and subsequent crystallization or by recrystallization of any Form of Clopidogrel hydrobromide from a suitable solvent or
15 mixture of solvents, comprising acetone, acetic acid ethyl ester, diisopropylether, tert.-butyl-methylether, methyl-isobutylketone, dichloromethane, Toluene, isobutyronitrile and/or isopropanol. Preferred is methyl-isobutylketone and/or isopropanol, preferably in a weight ration of 4:1, whereby crystallization is carried out within a temperature range
20 of -5°C to +15°C. Preferred are long crystallization and stirring times of the solution and suspensions, preferably longer than 24 hours.

The invention refers to a method of making of Clopidogrel
25 hydrobromide of Form F, which is characterized in that Clopidogrel hydrobromide of any crystalline Form is crystallized from a solvent or a mixture of solvents, comprising acetone, acetic acid ethyl ester, diisopropylether, tert.-butyl-methylether, methyl-isobutylketone, dichloro-
30 methane, toluene, isobutyronitrile and/or isopropanol, preferably methyl-isobutylketone and/or isopropanol, preferably in a weight ration of 4:1, within a temperature range of -5°C to +15°C.

Clopidogrel also forms salts with selected organic sulfonic acids. The present invention therefore also refers to the salts Clopidogrel besylate, Clopidogrel tosylate, and Clopidogrel napsylate as Form A and Form B, as well as to
5 Clopidogrel oxalate.

Clopidogrel besylate is obtained by combining equimolar amounts of benzenesulfonic acid and Clopidogrel base in a suitable solvent to react together. Suitable solvents are
10 for example alcohols, ethers and/or nitriles. Preferred as a solvent is methanol. Preferably the compound is isolated by solvent abstraction, i.e. for example by removing the solvent by distillation or by spray drying.

15 Clopidogrel tosylate is obtained by combining equimolar amounts of para-toluenesulfonic acid with Clopidogrel base in a suitable solvent to react together. Suitable solvents are for example alcohols, ethers and/or nitriles. Preferred as a solvent is methanol at a working temperature of 20-
20 25°C. Preferably the compound is isolated by solvent abstraction.

Clopidogrel napsylate Form A is obtained by combining equimolar amounts of naphthalene-2-sulfonic acid with Clopidogrel base in a suitable solvent and initiating crystallization by inoculating the crystallization solution with
25 Clopidogrel napsylate Form A. Suitable solvents are for example primary and secondary alcohols, ethers, nitriles, toluene and aqueous solvent mixtures, preferably thereof, with a water content of preferably less than 10% by weight
30 (<10% by weight). The suitable temperature working range is between 20°C and 60°C. Preferred solvents are isopropanol, water, diisopropylether, especially preferred is isopropanol. Alternatively Clopidogrel napsylate Form A is obtained
35 from other Clopidogrel salts (e.g. from Clopidogrel hydro-

bromide) by salt transformation in the presence of naphthalene-2-sulfonic acid salts (e.g. sodium-2-naphthylsulfonate). Suitable solvents are: isopropanol, diisopropylether, and aqueous solvent mixtures, preferably thereof, with a water content of preferably less than 10% by weight of water. The preferred working temperature range is also here 20°C to 60°C.

Clopidogrel napsylate Form A is obtained directly and without inoculation, by reacting equimolar amounts of naphthalene-2-sulfonic acid with Clopidogrel base in a suitable solvent, as described in the foregoing paragraph, wherein said naphthalene-2-sulfonic acid has a purity of at least 99.5 % by weight and preferably, wherein the content of sulfonic-1-sulfonic acid is less than 0.5% by weight.

Clopidogrel napsylate Form B is obtained by dissolving equimolar amounts of naphthalene-2-sulfonic acid with Clopidogrel base in a suitable solvent and initiating crystallization by inoculation with Clopidogrel napsylate Form B. Suitable solvents are primary and secondary alcohols, nitriles, toluene and/or aqueous solvent mixtures, preferably thereof, with a water content of preferably less than 10% by weight of water. Especially preferred is isopropanol as a solvent, a strongly over saturated crystallizing solution (>20%), a temperature working range from 15°C to 20°C, as well as prolonged mixing times of up to 24 hours (crystallization and mixing of the suspension).

Alternatively Clopidogrel napsylate Form B is also obtained by salt transformation from other Clopidogrel salts (e.g. Clopidogrel hydrobromide) in the presence of naphthalene-2-sulfonic acid salts (e.g. sodium-2-naphthylsulfonate) as well as by recrystallization from Clopidogrel napsylate Form A by inoculating the solution with the Form B. Suitable

solvents are isopropanol, diisopropylether, and aqueous solvent mixtures, preferably thereof, with a water content of preferably less than 10% by weight (<10% by weight) water, at a preferred temperature working range of 15°C to 20°C as well as prolonged mixing times of up to 24 hours (crystallizing and mixing of the suspension).

Clopidogrel napsylate Form B is obtained directly without inoculation by reacting equimolar amounts of naphthalene-2-sulfonic acid with Clopidogrel base in a suitable solvent, as described herein before, wherein the naphthalene-2-sulfonic acid used has a purity of less than 99.0% by weight and especially, if its content of naphthalene-1-sulfonic acid is higher than 1.0% by weight.

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The present invention refers to the compound Clopidogrel oxalate. Clopidogrel oxalate is obtained by reacting equimolar amounts of oxalic acid with Clopidogrel base in a suitable solvent. Suitable solvents are for example alcohols, ethers, nitriles, and/or aqueous solvent mixtures with a water content of preferably less than 10% by weight of water. Preferred solvents are isopropanol, diisopropylether and solvent mixtures, preferably thereof, with a water content of preferably less than 10% by weight of water (<10% by weight). Preferably the compound is isolated by solvent abstraction. In the previous cases mentioned, the condition that the water content is less than 10% by weight is a preferred but not a critical limitation.

30 Figures 1-11 show the XRPD diagram of Clopidogrel HBr Form A (Figure 1), Form B (Figure 2), Form C (Figure 3), Form D (Figure 4), Form E (Figure 5), Form F (Figure 6), Clopidogrel besylate (Figure 7), Clopidogrel tosylate (Figure 8), Clopidogrel napsylate Form A (Figure 9),
35 Clopidogrel napsylate Form B (Figure 10) und Clopidogrel

oxalate (Figure 11). The following examples illustrate the invention.

Example 1 (Clopidogrel hydrobromide of Form A)

- 5 160 g Clopidogrel base are dissolved in 260 g acetone.
Hydrogen bromide gas (HBr) is being introduced into this solution under ice cooling (inside temperature: 0°C - 5°C) until the pH-value of the solution (measured with humid indicator paper) is 2 (two). The formed suspension is left
10 to warm up to 20°C and is stirred for two hours. The solid is isolated using vacuum filtration and is washed with cold acetone. The humid product is dried under vacuum until it shows a constant weight. There are obtained 130 g Clopidogrel hydrobromide of Form A with the following properties:
15 HPLC content of Clopidogrel HBr: 100%
DSC: endothermic-maximum: 143°C

IR (KBr pressed mass) [cm^{-1} at % transmission]:

20	3484	67%;	3075	76%;	3005	58%;	2952	50%;	2704	59%;
	2628	46%;	2476	21%;	1753	3%;	1593	73%;	1474	37%;
	1437	17%;	1404	37%;	1349	42%;	1319	18%;	1297	20%;
	1226	8%;	1180	22%;	1135	55%;	1056	37%;	983	59%;
	965	45%;	919	65%;	885	75%;	845	46%;	789	61%;
25	762	24%;	740	30%;	706	51%;	626	86%;	597	72%;
	534	78%;	454	70%.						

XRPD [Cu $K\alpha_1$]:

Angle [$2\theta^\circ$]:	Relative intensity [%]
9.83	33
10.35	22
13.24	14
14.01	51
14.37	30
16.40	8
17.44	10
18.39	18
19.22	18
19.68	18
19.98	100
20.73	16

22.08	25
22.53	19
23.03	90
25.93	11
26.26	30
26.44	34
27.13	11
27.49	11
28.01	28
28.91	37
29.29	8
29.85	16
30.71	10
31.42	12
31.75	34
33.17	19
36.22	9
37.33	7
40.16	9
41.58	10
42.23	10
48.92	7

Example 2 (Clopidogrel hydrobromide of Form B)

10 g Clopidogrel hydrobromide are dissolved in 60 g acetone whereby the mixture is mildly warmed up until complete
 5 solution of the compound. The solution is evacuated under stirring in a large round bottom flask. A white residue of 10 g of Clopidogrel hydrobromide of the amorphous Form B is obtained with the following properties:

HPLC content of Clopidogrel HBr: 100%

10 DSC: endothermic-maximum: week minimum at about 130°C

IR (KBr pressed mass) [cm^{-1} at % transmission]:

3436 39%; 2952 50%; 2479 27%; 1754 3%; 1708 50%;
 1636 69%; 1480 38%; 1437 13%; 1320 26%; 1296 26%;
 15 1224 13%; 1179 25%; 1134 64%; 1056 46 1038 44%;
 1011 47%; 963 63%; 917 78%; 883 76%; 843 60%;
 788 68%; 762 26%; 727 41%; 627 79%; 597 65%;

531 76%; 455 67%.

XRPD [Cu K α_1]:

Angle [2 θ]:	Relative intensity [%]
9.50	34.95
10.39	34.57
12.87	24.42
13.74	23.08
14.14	38.5
16.13	31.84
16.86	20.24
18.52	18.04
19.53	100
20.88	44.26
21.63	20.92
22.34	18.09
22.93	47.93
23.23	52.29
23.60	17.76
24.83	32.92
25.12	47.4
25.41	40.78
27.25	24.32
27.54	26.55
28.50	25.57
29.01	30.56
30.07	16.68
30.67	19.36
31.23	19.37
31.53	14.47
32.26	29.23
33.57	15.51
34.16	10.02
36.09	10.93
36.83	12.91
40.70	11.28
44.15	11.06
48.63	8.98
9.50	34.95

Example 3 (Clopidogrel hydrobromide of Form C)

5 13 g Clopidogrel hydrobromide are stirred in 30 ml aceto-
nitrile for several hours at room temperature. The solid
material is then isolated by vacuum filtration. The humid
material is dried under vacuum until a constant weight. 11 g
Clopidogrel hydrobromide of Form C are obtained having the
10 following properties:

HPLC content of Clopidogrel HBr: 100%

DSC: endothermic-maximum: 145°C

IR (KBr pressed mass) [cm^{-1} at % transmission]:

15 3437 65%; 3064 48%; 3003 56%; 2952 51%; 2910 51%;
2533 24%; 1758 3%; 1593 77%; 1480 44%; 1439 21%;
1392 47%; 1348 44%; 1320 32%; 1295 12%; 1217 17%;
1178 18%; 1071 51%; 1031 44%; 1015 43%; 973 59%;
952 63%; 911 72%; 891 69%; 838 65%; 784 76%;
20 756 22%; 712 33%; 624 68%; 591 71%; 536 84%;
456 74%.

XRPD [Cu $\text{K}\alpha_1$]:

Angle [$2\theta^\circ$]:	Relative intensity [%]
8.20	63
8.92	100
13.91	21
14.76	21
15.07	22
16.67	52
18.52	45
19.42	17
20.49	22
21.31	27
21.62	23
22.49	14
22.88	25
23.31	28
24.46	74
25.83	55
26.87	25

27.60	25
27.96	21
28.81	15
29.66	18
30.60	22
32.67	22
37.51	11

Example 4 (Clopidogrel hydrobromide of Form D)

1 g Clopidogrel hydrobromide is stirred over night in 2 ml isopropanol at 40°C. The solid material is then isolated
 5 using vacuum filtration. The humid material is then dried under vacuum until constant weight. There are obtained 0.8 g Clopidogrel hydrobromide of Form D with the following properties:

HPLC content of Clopidogrel HBr: 100%

10 DSC: endothermic-maximum: 144°C

IR (KBr pressed mass) [cm^{-1} at % transmission]:

3483 58%; 3110 78%; 3075 82%; 3021 79%; 2906 61%;
 2486 30%; 2362 34%; 1753 3%; 1484 58%; 1436 29%;
 1391 47%; 1337 51%; 1316 46%; 1295 22%; 1260 47%;
 15 1228 19%; 1188 35%; 1136 72%; 1061 57%; 1035 51%;
 1009 45%; 967 66%; 944 63%; 903 72%; 845 69%;
 787 84%; 748 39%; 733 38%; 708 52%; 622 82%;
 597 76%; 542 91%; 484 87%; 454 80%.

20 XRPD [Cu $\text{K}\alpha_1$]:

Angle [$2\theta^\circ$]:	Relative intensity [%]
9.76	43
10.40	10
11.38	11
12.85	13
13.73	52
14.30	27
15.02	22
17.23	24
19.50	100
19.91	33
20.65	68

22.03	29
23.01	95
23.97	35
25.07	52
26.86	31
27.45	30
28.76	44
29.63	30
31.10	32

Example 5 (Clopidogrel hydrobromide of Form E)

13.5 g Clopidogrel hydrobromide are dissolved in 140 g dichloromethane. 82 g heptane (isomeric mixture) are added to the solution at room temperature and stirred over night under nitrogen gas. The solid material is isolated from the suspension obtained using vacuum filtration and is dried until constant weight. 13 g Clopidogrel hydrobromide of Form E are obtained having the following properties:

10 HPLC content of Clopidogrel HBr: 100%

DSC: endothermic-maximum: 125°C

IR (KBr pressed mass) [cm^{-1} at % transmission]:

3485 57%; 3007 64%; 2956 44%; 2908 41%; 2489 19%;
 1748 3%; 1593 75%; 1481 40%; 1438 18%; 1397 46%;
 15 1345 42%; 1321 31%; 1297 13%; 1263 43%; 1229 12%;
 1180 26%; 1059 52%; 1034 43%; 1015 33%; 968 65%;
 951 64%; 909 72%; 892 71%; 841 60%; 786 72%;
 758 24%; 720 17%; 623 72%; 593 73%; 539 87%;
 480 81%; 456 73%; 421 86%.

20 XRPD [$\text{Cu K}\alpha_1$]:

Angle [$2\theta^\circ$]:	Relative intensity [%]
7.72	41
9.27	47
9.88	65
11.91	51
14.28	41
15.45	42
16.91	34
20.65	32
21.10	59

21.38	71
22.17	50
23.15	68
24.11	86
25.36	52
25.87	100
26.96	43
28.74	64
29.74	39

Example 6 (Clopidogrel hydrobromide of Form F)

A mixture of 3500g isopropanol and 620g Clopidogrel hydrobromide of Form A are heated until a clear, slightly yellow solution is obtained (inside temperature (IT): 60°C-65°C). After quick cooling to an inside temperature of 10°C there crystallizes spontaneously, optionally after inoculation, a white powdery mass, which is isolated by vacuum filtration and is dried until constant weight. 361 g Clopidogrel hydrobromide of Form F are obtained having the following properties: HPLC content of Clopidogrel HBr: 100%; DSC: endothermic-maximum: 107.6°C

IR (KBr pressed mass) [cm^{-1} at % transmission]:

3325	16%	3113	46%	3067	61%	3013	53%	3001	51%
2961	50%	2889	57%	2858	57%	2725	55%	2479	37%
2349	57%	2299	60%	2142	66%	1956	81%	1744	3%
1613	58%	1588	63%	1573	77%	1493	49%	1470	26%
1453	26%	1434	19%	1423	15%	1390	52%	1364	60%
1351	41%	1334	30%	1322	28%	1285	29%	1276	33%
1257	29%	1239	23%	1222	29%	1211	19%	1188	30%
1171	23%	1093	66%	1056	30%	1043	39%	1028	41%
1011	28%	984	62%	965	57%	955	60%	930	73%
918	78%	906	57%	877	75%	865	69%	842	48%
826	77%	786	53%	762	8%	729	19%	715	44%
672	82%	637	70%	598	47%	590	43%	530	42%
505	58%	485	59%	457	47%	434	76%	425	69%

XRPD [Cu $\text{K}\alpha_1$]:

Angle [2 θ]:	Relative intensity [%]
8.95	19
9.74	27
12.48	82
13.83	34
15.89	66
16.67	28
17.99	25
18.84	20
19.53	54
20.02	80
20.16	100
20.52	56
20.86	21
21.52	33
21.97	94
22.32	22
23.35	42
24.20	45
24.65	18
25.46	32
26.16	36
26.36	45
27.91	73
28.44	54
31.28	25
32.14	28
33.33	31
34.91	25
36.43	12
37.85	16
41.01	13

Example 7 (Clopidogrel besylate)

3.0 g benzenesulfonic acid and 5.5 g Clopidogrel base are dissolved in 30 ml methanol. The solvent is evaporated in vacuum. 8.5 g Clopidogrel besylate are obtained with the following properties:

HPLC content of Clopidogrel besylate: 100%

DSC: endothermic-maximum: none

IR (KBr pressed mass) [cm^{-1} at % transmission]:

3437	28%;	3066	56%;	2957	42%;	2579	44%;	1752	3%;
1636	65%;	1593	76%;	1479	31%;	1444	14%;	1322	36%;
1226	3%;	1159	3%;	1122	4%;	1069	32%;	1034	11%;
1016	6%;	996	14%;	913	69%;	887	70%;	840	67%;
759	16%;	727	10%;	694	20%;	611	4%;	565	26%;
480	76%;	457	74%.						

XRPD [$\text{Cu K}\alpha_1$]: no clear peaks detectable

5 Example 8 (Clopidogrel tosylate)

3.2 g para-toluenesulfonic acid and 5.5 g Clopidogrel base are dissolved in 30 ml methanol. The solvent is evaporated by vacuum. There remain 8.7 g Clopidogrel tosylate with the following properties:

10 HPLC content of Clopidogrel besylate: 100%

DSC: endothermic-maximum: none

IR (KBr pressed mass) [cm^{-1} at % transmission]:

XRPD [$\text{Cu K}\alpha_1$]: no clear peaks detectable

15 Example 9 (Clopidogrel napsylate, Form A)

52.5 g sodium-2-naphthylsulfonate are dissolved in 430 ml dematerialized water under heating at about 75°C. A solution of 50 g Clopidogrel hydrogen sulfate in 200 ml water is added to the solution. The resulting mixture is cooled to room temperature and the upper oily phase is separated. The separated oil is dissolved in 230 g isopropanol. The obtained solution is dried with magnesium sulfate and diluted with 250 g diisopropylether. The solution is inoculated at a temperature of about 60°C with Clopidogrel napsylate and stirred over night whilst cooling to room temperature. The solid material is isolated by vacuum filtration, washed with diisopropylether and dried under vacuum. 37 g Clopidogrel napsylate of Form A are obtained with the following properties:

30 HPLC content of Clopidogrel napsylate: 100%

DSC: endothermic maximum: 149°C

IR (KBr pressed mass) [cm^{-1} at % transmission]:

3438	57%;	2969	47%;	2672	63%;	2593	59%;	2362	72%;
1751	10%;	1595	79%;	1475	54%;	1438	53%;	1329	54%;
1301	59%;	1222	11%;	1171	3%;	1135	29%;	1090	21%;
1032	10%;	993	60%;	956	78%;	906	82%;	886	83%;
866	74%;	830	64%;	783	83%;	753	27%;	724	76%;
698	48%;	676	21%;	650	71%;	623	73%;	597	76%;
567	47%;	480	69%;	461	76%;	421	78%.		

XRPD [$\text{Cu K}\alpha_1$]:

Angle [$2\theta^\circ$]:	Relative intensity [%]
6.79	32
8.27	33
8.59	59
12.44	21
12.62	22
13.07	31
13.55	62
16.87	59
17.24	63
18.25	14
19.00	71
19.69	52
20.02	19
20.24	47
21.34	100
21.82	17
22.40	42
22.72	19
23.02	50
23.27	25
23.65	47
24.75	49
25.09	33
25.34	56
25.85	18
27.11	25
27.61	19
28.12	22
32.14	15

32.55	20
32.97	14
35.10	11

Example 10 (Clopidogrel napsylate, Form A)

2.5 g sodium-2-naphthylsulfonate are dissolved in 60 ml of water. Suspended material is separated by filtration. 30 ml
5 methanol and 2.9 g Clopidogrel hydrobromide are then added. The solution obtained is vigorously stirred and put under slight vacuum and kept at room temperature until about 50% by weight of the solvent has slowly evaporated. The white solid thus formed is isolated by vacuum filtration, washed
10 with water and dried under vacuum until constant weight. 3 g Clopidogrel napsylate of Form A are obtained.

Example 11 (Clopidogrel napsylate, Form B)

A previously prepared hot solution (about 65°C) of 82g
15 Clopidogrel napsylate Form A in 462g isopropanol is cooled to 20-25°C and inoculated with Clopidogrel napsylate Form B. The mixture is well stirred during 24 hours at 15-20°C. The solid is then isolated from the suspension by vacuum filtration. The filter cake is washed with isopropanol at 15-20°C
20 and dried in air at an inside temperature of 20-25°C until constant weight is obtained. 70g Clopidogrel napsylate, Form B, are obtained.

DSC: endothermic-maximum: 114.4°C

XRPD [Cu K α 1]:

25

Angle [2 θ °]	Relative intensity [%]
7.67	21
8.41	100
9.05	27
10.00	34
11.58	30
15.03	25
16.39	35
16.86	18
17.41	20
17.75	26
18.35	36
18.75	48

19.21	85
19.91	47
20.81	23
21.70	37
22.78	21
23.33	27
23.95	36
25.01	30
25.35	27
25.95	27
26.13	45
26.69	27
28.29	23
30.36	17
33.65	15
34.62	16

Example 12 (Clopidogrel oxalate)

10 g Clopidogrel base and 3.1 g oxalic acid are dissolved in
100 ml dichloromethane. The solvent is evaporated under
5 vacuum. There remains 13 g Clopidogrel oxalate with the
following properties:

HPLC content of Clopidogrel oxalate: 100%

DSC: endothermic-maximum: none

10 Raman [cm⁻¹, intensity]:

1737.5	week	1621.8	medium	1594.1	week	1576.0	week	15
1514.5	medium	1498.7	medium	1451.5	medium	1396.7	week	13
1329.7	week	1316.3	week	1281.7	week	1252.5	week	12
1192.9	week	1167.5	week	1135.3	week	1089.5	week	10
1004.6	week	917.9	week	867.7	week	847.6	medium	8
785.9	week	764.0	week	718.4	medium	687.9	week	6
670.3	week	635.1	medium	609.5	week	584.9	week	5
542.7	week	534.5	week	506.0	week	486.8	week	4
432.1	week	410.3	week					

XRPD [Cu K α_1]: no distinct peaks are obtained.

15

Example 13 (Clopidogrel napsylate, Form A)

170 g Clopidogrel base and 115 g naphthalene-2-sulfonic acid
monohydrate are dissolved in 600 ml isopropanol at a 60°C
and slowly cooled. At 50°C the clear solution is inoculated

with Clopidogrel napsylate of Form A and further cooled at a rate of 10°C/h to room temperature. The crystals are isolated by vacuum filtration and dried under vacuum. There are obtained 223 g Clopidogrel napsylate of Form A.